PATENT COUPERATION TREATY

То:	Lúbûl	operty	DOT
LANE, Graham GLAXO WELLCOME PLC Glaxo Wellcome House Berkeley Avenue Greenford Middlesex UB6 0NN GRANDE BRETAGNE	13 FE	NOTIFICA	PCT TION OF TRANSMITTAL OF RNATIONAL PRELIMINARY AMINATION REPORT (PCT Rule 71.1)
Applicant's or agent's file reference		IMI	PORTANT NOTIFICATION
International application No. PCT/EP99/08186	International filing date (d. 01/11/1999	ay/month/year)	Priority date (day/month/year) 03/11/1998

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

Authorized officer

European Patent Office

Brell, S

D-80298 Munich

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Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465

Tel.+49 89 2399-7271

Form PCT/IPEA/416 (July 1992)

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference PG3602/WO F0			FOR FURTHER AC	TION		tion of Transmittal of Internat Examination Report (Form P		
International application No.			International filing date (d	ay/month/	year)	Priority date (day/month/ye	ar)	
PCT/EP	99/08	186	01/11/1999			03/11/1998	•	
Internation C07D47		ent Classification (IPC) or na	! tional classification and IPC					
Applicant			· · · · · · · · · · · · · · · · · · ·					
1	GLAXO GROUP LIMITED et al.							
 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 								
2. This	2. This REPORT consists of a total of 8 sheets, including this cover sheet.							
ļ b	This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).							
Thes	These annexes consist of a total of sheets.							
				•		•		
3. This r	report ⊠	contains indications rela	ting to the following item	s:	·			
H		Priority						
111	\boxtimes	Non-establishment of o	pinion with regard to nov	elty, inve	ntive step a	nd industrial applicability		
IV		Lack of unity of invention	n ,					
V	⊠	Reasoned statement un citations and explanation	ider Article 35(2) with req ns suporting such staten	gard to no	ovelty, inver	ntive step or industrial app	olicability;	
VI	\boxtimes	Certain documents cite	d			*		
VII	×	Certain defects in the in	ternational application					
VIII	VIII 🛛 Certain observations on the international application							
Date of sub	missio	n of the demand	. ,	Date of co	mpletion of th	nis report		
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	examii	address of the international ning authority:		Authorized	officer		STATE OF STATE VIEW	
)	D-80	pean Patent Office 298 Munich -49 89 2399 - 0 Tx: 523656	epmu d	Stellmad	ch, J		(an early and a second	
Fax: +49 89 2399 - 4465 Telephone No. +49 89 2399 8279							AND SOURCE SAND	



International application No. PCT/EP99/08186

I. Basis of the report

1	re th	This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).): Description, pages:									
	1-3	as originally filed									
	CI	aims, No.:									
	1-	16 as originally filed									
2.	Wi lan	th regard to the language , all the elements marked above were available or furnished to this Authority in the aguage in which the international application was filed, unless otherwise indicated under this item.									
	Th	ese elements were available or furnished to this Authority in the following language: , which is:									
		the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).									
	☐ the language of publication of the international application (under Rule 48.3(b)).										
		the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).									
3.	Wit	th regard to any nucleotide and/or amino acid sequence disclosed in the international application, the ernational preliminary examination was carried out on the basis of the sequence listing:									
		contained in the international application in written form.									
		filed together with the international application in computer readable form.									
•		furnished subsequently to this Authority in written form.									
		furnished subsequently to this Authority in computer readable form.									
		The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.									
		The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.									
ŀ.	The	e amendments have resulted in the cancellation of:									
		the description, pages:									
		the claims, Nos.:									
		the drawings, sheets:									
i.		This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):									

International application No. PCT/EP99/08186

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

									·		
6	Ade	ditional observations, if r	necessa	ıry:							
111	. No	n-establishment of opi	nion wi	th regard	i to novelt	y, inventi	ve step aı	nd induștri:	al applicat	oility	
1.	obv	e questions whether the vious), or to be industrial	ly applic	cable hav					ive step (to	be non-	·
		the entire international	applica	tion.			٠				
	☒	claims Nos. 13,14.									
be	ecaus	se:									
	Ø	the said international a not require an internati see separate sheet						following su	ıbject matte	er which o	does
		the description, claims that no meaningful opir					ents below) or said cla	ims Nos. a	are so un	ıclear
		the claims, or said clair could be formed.	ns Nos.	are so ir	nadequately	/ supporte	ed by the o	description t	hat no mea	aningful o	pinion
		no international search	report l	nas been	established	for the s	aid claims	Nos	•	:	
2.	and	neaningful international p Vor amino acid sequence ructions:	orelimina e listing	ary exami to comply	nation repo	rt cannot tandard pi	be carried rovided fo	l out due to r in Annex C	the failure	of the nuc ministrati	cleotid ve
		the written form has no	t been f	urnished (or does not	comply w	vith the sta	andard.			
		the computer readable	form ha	s not bee	n furnished	l or does i	not comply	y with the st	andard.		
٧.		soned statement unde					y, inventi	ve step or i	industrial	applicab	ility;
۱.		ement	• •								
	Nov	relty (N)	Yes: No:	Claims Claims	1-16						
	Inve	entive step (IS)	Yes: No:	Claims Claims	1-16						•
	Indu	strial applicability (IA)	Yes:	Claims	1-16					· .	

International application No. PCT/EP99/08186

No: Claims

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

INTERNATIONAL PRELIMINARY

International application No. PCT/EP99/08186

EXAMINATION REPORT - SEPARATE SHEET

SECTION	111	

- Claims 13 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34 (4) (a) (i) PCT).
- Under the terms of Rule 39.1 (iv) PCT, the International Preliminary Examination Authority is not required to carry out an examination of claims directed to a method of treatment of the human or animal body by surgery or therapy. As indicated in the Search Report, the search was carried out and based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

SECTION	V	
	v	

1. Prior art

Documents (1) - (8), which were cited in the International Search Report and the Written Opinion are considered to represent relevant prior art in this Preliminary Examination Report; the numbering will be adhered to in the rest of the procedure.

- (1) WO-A-99/12 930
- (2) WO-A-96/06 840
- /(3) WO-A-96/21 667
- (4) WO-A-96/31 509
 - (5) Bioorg.Med.Chem.Lett. <u>7</u>, 47 (1997)
 - (6) Bioorg.Med.Chem.Lett. <u>7</u>, 57 (1997)
- (7) Exp.Opin.Ther.Patents <u>7</u>, 55 (1997)
 - (8) Exp.Opin.Ther.Patents <u>8</u>, 21 (1998)

2.Novelty

- 2.1 Document (1) is only relevant for the purposes of **Rules 33.1 c, 64.3 and 70.10 PCT** (see also part VI, certain documents) and since the priority document is not available are not taken into account for the Preliminary Examination Report. If the priority date is not valid for the complete claimed subject-matter, document (1) may become relevant prior art in a possible regional / national phase.
- 2.2 Having regard to the available prior art (2) (8) the claimed subject-matter appears to fulfil the requirements of **Article 33 (2) PCT**, since the claimed substituted **pyrazolopyridine** derivatives differ from those of the prior art at least by the aza-bio-isosteric replacement of the 6-ring hetero cycle.

3. Inventive step

- 3.1 For the assessment of inventive step (Article 33 (3) PCT) of the claimed subject-matter, citation (2) is considered to represent the (respective) closest prior art. All the prior art documents (2) (8) disclose substituted imidazole/pyrazole diaryl derivatives being cyclooxygenase(COX)-inhibitors and their structural analogues.
- 3.2 Starting from the (respective) closest prior art (2), the technical problem underlying the application in suit (Article 33 (3) PCT, Rule 5.1 (a) (iii) PCT) can be considered to be the provision of different analogues (aza-isosteres) with unexpected pharmacological (COX) activity. Since the principle of aza-bioisosterism is well known in the field of cyclooxygenase(COX)-inhibitors 'inter alia' from citations (2) - (4), the skilled person having additionally a basic knowledge of the principles of structureactivity-relationships would expect the claimed compounds to be to cyclooxygenase inhibitors i.e. the claimed derivatives must be considered as close structural analogues of some mentioned in the prior art. The skilled person having knowledge of the teaching of the prior art would thus consider some of the claimed derivatives to be cyclooxygenase inhibitors at least to a certain degree. For the skilled person starting from the compounds disclosed in (2), (3) or (4) there is thus a clear incentive that the resulting compounds are cyclooxygenase inhibitors, since it is known from the structural modifications performed in the citations (2) - (8) that the principle of azabioisosterism can be applied without essentially changing the pharmacological activity. Having regard to the structural differences as described above vis-a-vis the prior art, this modification lies within the usual skill of the application of structure-activity-relationships. The skilled man would have been able to predict with certainty that the same pharmacological activity would be retained due to these structural modifications. There is thus a rea-

EXAMINATION REPORT - SEPARATE SHEET

sonable expectation of success to arrive at compounds being cyclooxygenase inhibitors. Accordingly, at present the requirements of Article 33 (3) PCT are not met. Given the properties to be expected for the claimed compounds (analogues) in comparison with those of the prior art, an inventive step could be recognized if the Applicant could demonstrate that the presently claimed compounds illustrate any unpredictable (qualitatively or quantitatively) pharmacological activity. The pharmacological tests performed with some of the claimed compounds (see pages 34/35) cannot be taken into account, since the cyclooxygenase inhibition (even selectivity, see citations (2) and (4) - (6)) is not surprising.

3.3 Finally, it is realized that the Applicant is entitled to claim all obvious modifications of what he has described and that alternative variations have to be supported by a certain number of examples. Furthermore, the extent of a "reasonable generalisation" only depends upon the question of the relative distance to the prior art compounds. It is stressed that only such compounds can be claimed which are a solution to the above stated problem i.e. which illustrate the alleged unexpected pharmacological activity.

4. Industrial applicability

- 4.1 No objection re industrial applicability of claims 1 - 12, 15 and 16 arises insofar the claimed compounds would exhibit the alleged unexpected pharmacological properties (Article 33 (4) PCT).
- 4.2 For the assessment of the present claims 13 and 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION \	/

Certain published documents (Rule 70.10)

INTERNATIONAL PRELIMINARY

International application No. PCT/EP99/08186

EXAMINATION REPORT - SEPARATE SHEET

Application No Patent No	Publication date (day/month/year)	<u>Filing date</u> (<u>day/month/year)</u>	Priority date (valid claim) (day/month/year)						
WO-A-99/12930	18.3.99	3.9.98	5.9.97						
			23.12.97						

SECTION VII									

- Since the documents (1) (8) were not identified in the description and the relevant background art disclosed therein was not briefly discussed, the requirements of Rule 5.1 (a) (ii) PCT are not met.
- The dependent claims are only possible as specific form in conjunction with in-2. dependent claims of the invention (Rule 6.4 PCT).

SECTION VIII-----

The Applicant is informed that the breadth of the claims has to be such that it comprises only variants which are able to solve the problem underlying the invention being a prerequisite for the acknowledgement of inventive step (Article 33 (3) PCT).

Litery,

REQUEST

For receiving Office use only
International Application No. 9 / 08 186
International Filing Date NOV 1999 (0 1. 11. 99)
EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT In' Application"
Applicant's or agent's file reference (if desired) (12 characters maximum) PG3602

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The undersigned requests that the present	EUROFEAN PATENT OFFICE						
international application be processed	PCT INTERNATIONAL APPLICATION						
according to the Patent Cooperation Treaty	Name of receiving Office and "PCT In' Application"						
	Applicantly or county 51 5						
•	Applicant's or agent's file reference (if desired) (12 characters maximum) PG3602						
BIX No. 1 TITLE OF INVENTION							
PYRAZOLOPYRIL	DINE DERIVATIVES						
Бах No. II APPLICANT							
Name and achiress: (Family name followed by given name; for a legal en	tity, full official						
resignation. The address must include postal code and name of country. The indicated in ris Box is the applicant's State (that is, country) of residence if r	re country of the address This person is also inventor.						
micaed beow,	Telephone No. 0171 493 4060						
zxo Group Limited	·						
Caxo Wellcome House	Facsimile No. 0181 966 8838						
Berkeley Avenue	Teleprinter No. 25456						
Camford, Middlesex, UB6 0NN	receptimes No. 23430						
<u>GB</u>							
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Bix No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS							
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Further applicants and/or (further) inventors are indicated on a							
BIX No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE							
The person identified below is hereby/has been appointed to act on behalf in the explicants) before the competent International Authorities as:							
Name and address: (Family name followed by given name; for a legal ent	tity, full official Telephone No.:						
assignation. The address must include postal code and name of con	untry). 0171-493-4060						
LANE, Graham	Facsimile No.:						
Gaxe Wellcome plc 0181-966-8838							
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Further applicants and/or (further) inventors are indicated on a continuation sheet.

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Precamionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excended from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn in the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the parameter of the designation and confirmation must reach the receiving Office within the 15-month time limit.)

Sheet No ..4...

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timely received the purported i	d papers or o	frawings comp	leting		•			
Date of timely corrections und							.	not received:
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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7:

C07D 471/04, A61K 31/435 // (C07D 471/04, 231:00, 221:00)

A1

(11) International Publication Number:

WO 00/26216

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11 May 2000 (11.05.00)

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1 November 1999 (01.11.99)

(30) Priority Data:

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3 September 1999 (03.09.99) G

(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

- (75) Inventors/Applicants (for US only): CAMPBELL, Ian, Baxter [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). NAYLOR, Alan [GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).
- (74) Agent: LANE, Graham, Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PYRAZOLOPYRIDINE DERIVATIVES AS SELECTIVE COX-2 INHIBITORS

$$R^3O_2S$$
 R^0
 R^1
 R^1
 R^2
 R^3
 R^2
 R^3
 R^2
 R^3
 R^3

(57) Abstract

The invention provides the compounds of formula (I) and pharmaceutically acceptable derivatives thereof in which: R^0 and R^1 are independently selected from H, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, or C_{1-6} alkoxy substituted by one or more fluorine atoms; R^2 is H, C_{1-6} alkyl, C_{1-6} alkyl substituted by one or more fluorine atoms, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6}

Express Mail₋Label No.: EL395890988US

From the INTERNATIONAL SEARCHING AUTHORITY To: NOTIFICATION OF TRANSMITTAL OF GLAXO WELLCOME PLCitor of intellectual Property THE INTERNATIONAL SEARCH REPORT Glaxo Wellcome House... OR THE DECLARATION INIT Attn. Lane, Grahamanal -1 MAR 2000 Berkeley Avenue (PCT Rule 44.1) Greenford Middlesex UB6 ONN 4111 FILE UNITED KINGDOM TcDate of mailing (day/month/year) **28/02/2000** ~ Applicant's or agent's file reference FOR FURTHER ACTION PG3602 See paragraphs 1 and 4 below International application No. International filing date (day/month/year) PCT/EP 99/08186 01/11/1999 Applicant GLAXO GROUP LIMITED et al. 1. X The applicant is hereby notified that the International Search Report has been established and is transmitted herewith. Filing of amendments and statement under Article 19: The applicant is entitled, if he so wishes, to amend the claims of the international Application (see Rule 46): The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet. Where? Directly to the International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Fascimile No.: (41-22) 740.14.35 For more detailed instructions, see the notes on the accompanying sheet. The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that: the protest together with the decision thereon has been transmitted to the international Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices. no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made. Further action(s): The applicant is reminded of the following: Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the international Bureau as provided in Rules 90bs.1 and 90bs.3, respectively, before the completion of the technical preparations for international publication. Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later). Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentiaan 2

NL-2280 HV Rijewijk

Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Véronique Baillou

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

Notes to Form PCT/ISA/220 (first sheet) (January 1994)

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed:
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:
 "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
- [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
 "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
 "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

it must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.



(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER see Notification of	of Transmittal of International Search Report					
PG3602	ACTION	20) as well as, where applicable, item 5 below.					
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)					
PCT/EP 99/08186	01/11/1999	03/11/1998					
Applicant							
GLAXO GROUP LIMITED et al							
This international Search Report has been according to Article 18. A copy is being tra	n prepared by this international Searching Auti unamitted to the International Bureau.	nority and is transmitted to the applicant					
This international Search Report consists	of a total of 3 sheets.						
	a copy of each prior art document cited in this	report.					
Basis of the report							
a. With regard to the language, the i	international search was carried out on the bases otherwise indicated under this item.	sis of the international application in the					
the International search w. Authority (Rule 23.1(b)).	as carried out on the basis of a translation of ti	ne international application furnished to this					
b. With regard to any nucleotide and was carried out on the basis of the	d/or amino acid sequence disclosed in the in	ternational application, the international search					
	nal application in written form.						
filed together with the inte	mational application in computer readable form	n.					
furnished subsequently to	this Authority in written form.						
furnished subsequently to	this Authority in computer readble form.						
the statement that the sub international application as	sequently fumished written sequence listing do s filed has been fumished.	oes not go beyond the disclosure in the					
the statement that the info furnished	mation recorded in computer readable form is	identical to the written sequence listing has been					
2. Certain claims were four	nd unsearchable (See Box I).						
3. Unity of invention is lack	3. Unity of invention is lacking (see Box II).						
4. With regard to the title,							
the text is approved as suf	omitted by the applicant.						
the text has been established by this Authority to read as follows:							
PYRAZOLOPYRIDINE DERIV	ATIVES AS SELECTIVE COX-2 1	NHIBITORS					
5. With regard to the abstract,							
the text is approved as suf							
the text has been establish within one month from the	ned, according to Rule 38.2(b), by this Authorit date of mailing of this international search rep	y as it appears in Box III. The applicant may, ort, submit comments to this Authority.					
6. The figure of the drawings to be public	•						
	as suggested by the applicant. X None of the figures.						
because the applicant falls	d to suggest a figure.						
because this figure better	characterizes the invention.						

Form PCT/ISA/210 (first sheet) (July 1998)



International Application No F/EP 99/08186

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/435 //(C07D471/04,231:00,221:00)

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 C070

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
P,X	WO 99 12930 A (NAYLOR ALAN ;BESWICK PAUL (GB); CAMPBELL IAN (GB); GLAXO GROUP LTD) 18 March 1999 (1999-03-18) the whole document	1-16			
Υ	WO 96 06840 A (MERCK FROSST CANADA INC; PRASIT PETPIBOON (CA); GUAY DANIEL (CA);) 7 March 1996 (1996-03-07) * see exs. 4 and 5 and last 3 exs. on page 31 * the whole document	1-16			
Υ	WO 96 31509 A (GLAXO GROUP LTD ;BESWICK PAUL JOHN (GB); CAMPBELL IAN BAXTER (GB);) 10 October 1996 (1996-10-10) the whole document	1-16			
	-/				

Patent family members are listed in annex.
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the
document is combined with one or more other such docu- ments, such combination being obvious to a person sidiled in the art. "&" document member of the same patent family
Date of mailing of the International search report 28/02/2000
Authorized officer Stellmach, J



T/EP 99/08186

C.(Continue	ition) DOCUMENTS CONSIDERED TO BE RELEVANT	1/21 99/08180
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to dam No.
Y	WO 96 21667 A (MERCK FROSST CANADA INC ;GAUTHIER JACQUES YVES (CA); LAU CHEUK K () 18 July 1996 (1996-07-18) the whole document	1-16
Y	THERIEN M ET AL: "Synthesis and biological evaluation of 5,6-diarylimidazo'2.1-b!thiaz ole as selective COX-2 inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 7, no. 1, 7 January 1997 (1997-01-07), pages 47-52, XP004135964 ISSN: 0960-894X the whole document	1-16
Y	ROY P ET AL: "A new series of selective COX-2 inhibitors: 5,6-diarylthiazolo'3,2-b! '1,2,4!triazoles" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 7, no. 1, 7 January 1997 (1997-01-07), pages 57-62, XP004135966 ISSN: 0960-894X the whole document	1-16
Y	TALLEY J J: "Selective inhibitors of cyclooxygenase-2" EXPERT OPINION ON THERAPEUTIC PATENTS,GB,ASHLEY PUBLICATIONS, vol. 7, no. 1, 1 January 1997 (1997-01-01), pages 55-62, XP002086250 ISSN: 1354-3776 * see page 59, cpds. 13-15 * the whole document	1-16
Y	CARTER J S: "Recently reported inhibitors of cyclooxygenase-2" EXPERT OPINION ON THERAPEUTIC PATENTS,GB,ASHLEY PUBLICATIONS, vol. 8, no. 1, 1 January 1998 (1998-01-01), pages 21-29, XP002086251 ISSN: 1354-3776 the whole document	1–16

rmation on patent family members

International Application No CT/EP 99/08186

	ent document n search repor	t	Publication date		Patent family member(s)	Publication date
WO 9	912930	Α	18-03-1999	AU	9439598 A	29-03-1999
WO 9	606840	A	07-03-1996	US	5521213 A	28-05-1996
				AU	689302 B	26-03-1998
				AU	3249295 A	22-03-1996
				CA	2197895 A	07-03-1996
				EP	0778834 A	18-06-1997
				JP	10504829 T	12-05-1998
WO 9	631509	Α	10-10-1996	AU	5276696 A	23-10-1996
				BG	101934 A	30-04-1999
			•	BR	9604870 A	26-05-1998
				CA	2216809 A	10-10-1996
			•	CN	1186492 A	01-07-1998
				CZ	9703133 A	18-03-1998
				EP	0819127 A	21-01-1998
				HÜ	9801602 A	30-11-1998
		•		JP	11501049 T	26-01-1999
				NO	974595 A	03-12-1997
				NZ	304886 A	25-11-1998
				PL	322623 A	02-02-1998
	·			SK	133297 A	08-07-1998
WO 9	621667	A	18-07-1996	US	5552422 A	03-09-1996
				AU	697650 B	15-10-1998
				AU	4381496 A	31-07-1996
				CA	2209895 A	18-07-1996
				EP.	0802917 A	29-10-1997
				JP	11501902 T	16-02-1999



REC'D 13 FEB 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's o	r agei	nt's file reference		See Notifica	ation of Transmittal of International
PG3602/V	VO		FOR FURTHER ACT	FION Preliminary	Examination Report (Form PCT/IPEA/416)
International	applic	cation No.	International filing date (da	ay/month/year)	Priority date (day/month/year)
PCT/EP99	9/081	186	01/11/1999		03/11/1998
International C07D471/		nt Classification (IPC) or na	tional classification and IPC		
Applicant					
GLAXO G	ROL	JP LIMITED et al.			
		tional preliminary exam mitted to the applicant a		repared by this Inte	rnational Preliminary Examining Authority
2. This R	EPO	RT consists of a total of	8 sheets, including this	cover sheet.	
be (so	een a ee Ri anne	mended and are the basule 70.16 and Section 6	sis for this report and/or s 07 of the Administrative I	sheets containing re nstructions under th	n, claims and/or drawings which have ctifications made before this Authority ne PCT).
	_				
1		Basis of the report			
11 111		Priority Non-ostablishment of o	ninion with regard to no	elty inventive sten	and industrial applicability
IV		Lack of unity of invention	-	reity, inventive step	and modernal approaching
, V		Reasoned statement u		gard to novelty, inve	entive step or industrial applicability;
VI	×	Certain documents cit	ed ·		
· VII	Ø	Certain defects in the i	nternational application		
Aili	\boxtimes	Certain observations o	n the international applic	ation	
Date of subr	nissic	n of the demand		Date of completion of	this report
27/04/200	00			09.02.2001	•
		g address of the internationa	al	Authorized officer	ST ASCHES MATCH COM

Stellmach, J

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European Patent Office D-80298 Munich

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Tel. +49 89 2399 - 0 Tx: 523656 epmu d

International application No. PCT/EP99/08186

I.	Basi	s of	the	re	port
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res _i the		s report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in ponse to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to report since they do not contain amendments (Rules 70.16 and 70.17).): scription, pages:							
	1-35	5	as originally filed						
	Clai	ms, No.:							
	1-16	3	as originally filed						
2.	With	n regard to the lang guage in which the i	puage, all the elements marked above were available or furnished to this Authority in the international application was filed, unless otherwise indicated under this item.						
	The	se elements were a	available or furnished to this Authority in the following language: , which is:						
		• •	translation furnished for the purposes of the international search (under Rule 23.1(b)).						
		the language of pu	iblication of the international application (under Rule 48.3(b)).						
		the language of a 55.2 and/or 55.3).	translation furnished for the purposes of international preliminary examination (under Rule						
3.			electide and/or amino acid sequence disclosed in the international application, the y examination was carried out on the basis of the sequence listing:						
		contained in the in	ternational application in written form.						
		filed together with	the international application in computer readable form.						
		furnished subsequ	ently to this Authority in written form.						
		furnished subsequ	ently to this Authority in computer readable form.						
			t the subsequently furnished written sequence listing does not go beyond the disclosure in pplication as filed has been furnished.						
		The statement that listing has been full	t the information recorded in computer readable form is identical to the written sequence rnished.						
4.	The	amendments have	e resulted in the cancellation of:						
		the description,	pages:						
		the claims,	Nos.:						
		the drawings,	sheets:						
5.			een established as if (some of) the amendments had not been made, since they have been beyond the disclosure as filed (Rule 70.2(c)):						

International application No. PCT/EP99/08186

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

3.	Add	itional observations, if ne	cessary	:								
III.	Non	n-establishment of opini	on with	regard t	o novel	ty, inven	tive ste	p and ind	ustrial a	pplicab	ility	
1.	obvi	questions whether the clious), or to be industrially	applica	ble have	appears not bee	to be nov	vel, to in ed in res	volve an i	nventive	step (to	be non-	
		the entire international applications Nos. 13,14.	pplicatio	n.								
be	caus	se:										
	×	the said international approximation require an internation see separate sheet	plication nal preli	, or the s minary ex	aid clain kaminati	ns Nos. r on (<i>speci</i>	relate to ify):	the follow	ing subje	ect matte	er which	does
		the description, claims o that no meaningful opinion	r drawir on could	igs (<i>indic</i> d be form	ate parti ed (spec	icular elei cify):	ments b	<i>elow</i>) or sa	aid claim	s Nos.	are so ui	nclear
		the claims, or said claim could be formed.	s Nos.	are so ina	adequat	ely suppc	orted by	the descri	ption tha	t no me	aningful	opinion
		no international search r	eport ha	as been e	stablish	ed for the	e said cl	aims Nos.				
2.	and	neaningful international pr Vor amino acid sequence tructions:	eliminar listing t	y examin o comply	ation re with the	port cann standard	ot be ca d provide	arried out o ed for in A	due to the nnex C o	e failure of the Ac	of the no Iministra	ucleotid tive
		the written form has not	been fu	rnished c	r does r	not compl	ly with th	ne standar	d.			
		the computer readable f	orm has	not beer	n furnish	ed or do	es not co	omply with	the star	idard.		
V.		asoned statement under ations and explanations					velty, in	ventive s	tep or in	dustria	l applica	bility;
1.	Sta	tement										
	Nov	velty (N)	Yes: No:	Claims Claims	1-16							
	Inv	entive step (IS)	Yes: No:	Claims Claims	1-16							
	Ind	ustrial applicability (IA)	Yes:	Claims	1-16							

International application No. PCT/EP99/08186

No: Claims

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

SECTION III -----

- 1. Claims 13 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34 (4) (a) (i) PCT).
- 2. Under the terms of Rule 39.1 (iv) PCT, the International Preliminary Examination Authority is not required to carry out an examination of claims directed to a method of treatment of the human or animal body by surgery or therapy. As indicated in the Search Report, the search was carried out and based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

SECTION	V	
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1. Prior art

Documents (1) - (8), which were cited in the **International Search Report** and the **Written Opinion** are considered to represent relevant prior art in this **Preliminary Examination Report**; the numbering will be adhered to in the rest of the procedure.

- (1) WO-A-99/12 930
- (2) WO-A-96/06 840
- (3) WO-A-96/21 667
- (4) WO-A-96/31 509
- (5) Bioorg.Med.Chem.Lett. <u>7</u>, 47 (1997)
- (6) Bioorg.Med.Chem.Lett. <u>7</u>, 57 (1997)
- (7) Exp.Opin.Ther.Patents <u>7</u>, 55 (1997)
- (8) Exp.Opin.Ther.Patents <u>8</u>, 21 (1998)

INTERNATIONAL PRELIMINARY Inte

2.Novelty

- 2.1 Document (1) is only relevant for the purposes of **Rules 33.1 c, 64.3 and 70.10 PCT** (see also part VI, certain documents) and since the priority document is not available are not taken into account for the Preliminary Examination Report. If the priority date is not valid for the complete claimed subject-matter, document (1) may become relevant prior art in a possible regional / national phase.
- 2.2 Having regard to the available prior art (2) (8) the claimed subject-matter appears to fulfil the requirements of **Article 33 (2) PCT**, since the claimed substituted **pyrazolopyridine** derivatives differ from those of the prior art at least by the aza-bio-isosteric replacement of the 6-ring hetero cycle.

3. Inventive step

- 3.1 For the assessment of inventive step (Article 33 (3) PCT) of the claimed subject-matter, citation (2) is considered to represent the (respective) closest prior art. All the prior art documents (2) (8) disclose substituted imidazole/pyrazole diaryl derivatives being cyclooxygenase(COX)-inhibitors and their structural analogues.
- Starting from the (respective) closest prior art (2), the technical problem un-3.2 derlying the application in suit (Article 33 (3) PCT, Rule 5.1 (a) (iii) PCT) can be considered to be the provision of different analogues (aza-isosteres) with unexpected pharmacological (COX) activity. Since the principle of aza-bioisosterism is well known in the field of cyclooxygenase(COX)-inhibitors 'inter alia' from citations (2) - (4), the skilled person having additionally a basic knowledge of the principles of structureactivity-relationships would expect the claimed compounds to be to cyclooxygenase inhibitors i.e. the claimed derivatives must be considered as close structural analogues of some mentioned in the prior art. The skilled person having knowledge of the teaching of the prior art would thus consider some of the claimed derivatives to be cyclooxygenase inhibitors at least to a certain degree. For the skilled person starting from the compounds disclosed in (2), (3) or (4) there is thus a clear incentive that the resulting compounds are cyclooxygenase inhibitors, since it is known from the structural modifications performed in the citations (2) - (8) that the principle of azabioisosterism can be applied without essentially changing the pharmacological activity. Having regard to the structural differences as described above vis-a-vis the prior art, this modification lies within the usual skill of the application of structure-activity-relationships. The skilled man would have been able to predict with certainty that the same pharmacological activity would be retained due to these structural modifications. There is thus a rea-

sonable expectation of success to arrive at compounds being cyclooxygenase inhibitors. Accordingly, at present the requirements of Article 33 (3) PCT are not met. Given the properties to be expected for the claimed compounds (analogues) in comparison with those of the prior art, an inventive step could be recognized if the Applicant could demonstrate that the presently claimed compounds illustrate any unpredictable (qualitatively or quantitatively) pharmacological activity. The pharmacological tests performed with some of the claimed compounds (see pages 34/35) cannot be taken into account, since the cyclooxygenase inhibition (even selectivity, see citations (2) and (4) - (6)) is not surprising.

3.3 Finally, it is realized that the Applicant is entitled to claim all obvious modifications of what he has described and that alternative variations have to be supported by a certain number of examples. Furthermore, the extent of a "reasonable generalisation" only depends upon the question of the relative distance to the prior art compounds. It is stressed that only such compounds can be claimed which are a solution to the above stated problem i.e. which illustrate the alleged unexpected pharmacological activity.

4. Industrial applicability

- 4.1 No objection re industrial applicability of claims 1 12, 15 and 16 arises insofar the claimed compounds would exhibit the alleged unexpected pharmacological properties (**Article 33 (4) PCT**).
- 4.2 For the assessment of the present claims 13 and 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION	VI	

Certain published documents (Rule 70.10)

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/08186

Application No

Publication date (day/month/year)

Filing date (day/month/year) Priority date (valid claim) (day/month/year)

WO-A-99/12930

Patent No

18.3.99

3.9.98

5.9.97

23.12.97

SECTION VII -----

- Since the documents (1) (8) were not identified in the description and the rele-1. vant background art disclosed therein was not briefly discussed, the requirements of Rule 5.1 (a) (ii) PCT are not met.
- The dependent claims are only possible as specific form in conjunction with in-2. dependent claims of the invention (Rule 6.4 PCT).

SECTION VIII-----

The Applicant is informed that the breadth of the claims has to be such that it comprises only variants which are able to solve the problem underlying the invention being a prerequisite for the acknowledgement of inventive step (Article 33 (3) PCT).

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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PG3602		f Transmittal of International Search Report 20) as well as, where applicable, Item 5 below.
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/EP 99/08186	01/11/1999	03/11/1998
Applicant		
GLAXO GROUP LIMITED et al	•	
This international Search Report has been according to Article 18. A copy is being tra	n prepared by this international Searching Auth	norfty and is transmitted to the applicant
This international Search Report consists It is also accompanied by	of a total of sheets. a copy of each prior art document cited in this	report.
Basis of the report		
	international search was carried out on the bas ass otherwise indicated under this item.	sis of the international application in the
the International search w Authority (Rule 23.1(b)).	as carried out on the basis of a translation of the	ne international application furnished to this
was carried out on the basis of the	e sequence listing:	ternational application, the international search
	nal application in written form.	•
)	mational application in computer readable form this Authority in written form.	1.
	this Authority in computer readble form.	
the statement that the sub	sequently furnished written sequence listing do s filed has been furnished.	oes not go beyond the disclosure in the
the statement that the info furnished	rmation recorded in computer readable form is	Identical to the written sequence listing has been
2. Certain claims were four	nd unsearchable (See Box I).	
3. Unity of invention is laci	dng (see Box II).	
4. With regard to the title,		
the text is approved as su		
	hed by this Authority to read as follows: 'ATIVES AS SELECTIVE COX-2 1	MUTDITADO
TIMAZOLOFINIDINE DENT	ATTVES AS SELECTIVE COX-2 I	IMITELIONS
5. With regard to the abstract,		
	omitted by the applicant. hed, according to Rule 38.2(b), by this Authorit date of mailing of this international search rep	
6. The figure of the drawings to be publi	shed with the abstract is Figure No.	
as suggested by the application	cant.	X None of the figures.
because the applicant fall		
because this figure better	characterizes the invention.	

ernational Application No CT/EP 99/08186

A. CLASSIFICATION OF SUBJECT MATTER
1PC 7 C07D471/04 A61K31/435 //(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) $IPC \ 7 \ CO7D$

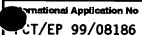
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

P,X	Citation of document, with indication, where appropriate, of the relevant passages WO 99 12930 A (NAYLOR ALAN ; BESWICK PAUL (GB); CAMPBELL IAN (GB); GLAXO GROUP LTD) 18 March 1999 (1999-03-18) the whole document WO 96 06840 A (MERCK FROSST CANADA INC	Relevant to claim No. 1-16
Υ Υ	(GB); CAMPBELL IAN (GB); GLAXO GROUP LTD) 18 March 1999 (1999-03-18) the whole document	1-16
Y	WO 96 06840 A (MERCK FROSST CANADA INC	
	;PRASIT PETPIBOON (CA); GUAY DANIEL (CA);) 7 March 1996 (1996-03-07) * see exs. 4 and 5 and last 3 exs. on page 31 * the whole document	1-16
Y	WO 96 31509 A (GLAXO GROUP LTD ;BESWICK PAUL JOHN (GB); CAMPBELL IAN BAXTER (GB);) 10 October 1996 (1996-10-10) the whole document	1-16
	-/	

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.			
Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention. "X" document of particular relevance; the cialmed invention carnot be considered novel or carnot be considered to involve an inventive step when the document is taken alone. "Y" document of particular relevance; the cialmed invention carnot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family			
Date of the actual completion of the international search	Date of mailing of the international search report			
18 February 2000	28/02/2000			
Name and mailing address of the ISA	Authorized officer			
European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016	Stellmach, J			

2



		CT/EP 99/08186
C.(Continu	ection) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 21667 A (MERCK FROSST CANADA INC ;GAUTHIER JACQUES YVES (CA); LAU CHEUK K () 18 July 1996 (1996-07-18) the whole document	1-16
Y	THERIEN M ET AL: "Synthesis and biological evaluation of 5,6-diarylimidazo'2.1-b!thiaz ole as selective COX-2 inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 7, no. 1, 7 January 1997 (1997-01-07), pages 47-52, XP004135964 ISSN: 0960-894X the whole document	1-16
Y	ROY P ET AL: "A new series of selective COX-2 inhibitors: 5,6-diarylthiazolo'3,2-b! '1,2,4!triazoles" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 7, no. 1, 7 January 1997 (1997-01-07), pages 57-62, XP004135966 ISSN: 0960-894X the whole document	1-16
Y	TALLEY J J: "Selective inhibitors of cyclooxygenase-2" EXPERT OPINION ON THERAPEUTIC PATENTS,GB,ASHLEY PUBLICATIONS, vol. 7, no. 1, 1 January 1997 (1997-01-01), pages 55-62, XP002086250 ISSN: 1354-3776 * see page 59, cpds. 13-15 * the whole document	1-16
Y	CARTER J S: "Recently reported inhibitors of cyclooxygenase-2" EXPERT OPINION ON THERAPEUTIC PATENTS,GB,ASHLEY PUBLICATIONS, vol. 8, no. 1, 1 January 1998 (1998-01-01), pages 21-29, XP002086251 ISSN: 1354-3776 the whole document	1-16

mation on patent family members

ernational Application No CT/EP 99/08186

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				PL	32262		02-02-1998
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				CA	220989		18-07-1996
				EP	080291		29-10-1997
				JP	1150190	2 T	16-02-1999